REMARKS

In the Office Action Mailed March 6, 2007, the Examiner rejected claims 1–6 on the ground of nonstatutory obviousness-double patenting as being unpatentable over claims 1-2, 7 and 8-10 of US Patent No. 6,489,467. In addition, claims 1-9 were rejected under 35 U.S.C. § 112, second paragraph, and claims 1-9 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Carlino et al. in view of Sakuma et al. For the reasons that follow, Applicant traverses these grounds for rejecting the claims of the present application.

Claims 1, 3 and 6 have been amended to address the Examiner's claim rejections under 35 U.S.C. § 112. It is considered that these objections are fully traversed by the amended claims.

The Examiner's rejection of the pending claims on grounds of double-patenting over US Patent No. 6,489,467, or, alternatively, of obviousness over the earlier Medidom PCT application, WO 00/44925, of which US Patent No. 6,489,467 is the US national phase equivalent, in view of the European patent application EP 0 631 799, cannot be supported. It is respectfully submitted that the Examiner's rejections are based solely on unallowable hindsight. In this regard, please consider the following.

It is highlighted that the present invention is directed to a method for preparing a sterile ready-to-use aqueous pharmaceutical formulation comprising a high molecular weight hyaluronic acid salt (HA) at a specified concentration. Previously used methods for the preparation of ready-to-use pharmaceutical formulations of hyaluronic acid involve measuring a defined precise quantity by weight of hyaluronic acid that is mixed with a precise volume of water and precise quantities of excipients. The formulation is then filled into syringes and vials, and subsequently sterilized by autoclave, with the associated problems of degradation of HA molecular chains on heat sterilization. Even where the preparation of the ready-to-use aqueous formulation of hyaluronic acid salt is carried out starting from a pre-sterilized powder of hyaluronic acid salt, this HA powder must be measured in an accurate amount and added to a precise quantity of water, and precise amounts of excipients, in order to get the required accurate concentration of the pharmaceutical formulation necessary for medical applications. The measuring and mixing of the sterilized HA powder necessarily requires removal of the sterilized

powder from the storage vessel transfer to a measuring vessel, and to the vessel in which it will be mixed with water. In all of these steps there is introduced a risk of contamination of the sterile powder.

An alternative process for preparing ready-to-use hyaluronic acid pharmaceutical formulations is reported in US Patent No. 5,093,487 (cited in the present application), which involves filtering a concentrated solution of hyaluronic acid aqueous formulation by means of multiple passes through a 0.2 μm filter so as to irreversibly reduce the viscosity of the hyaluronic acid. The process of US Patent No. 5,093,487 not only causes an irreversible reduction of the viscosity of, but it is also not possible to control the homogeneous viscosity of the HA solution after such multiple filtration steps, such that viscosity variations may occur from one batch of hyaluronic acid formulation to another. This irreversible reduction of the viscosity of the hyaluronic acid, and the variability of viscosity of batches of sterilised formulation, are undesirable for pharmaceutical applications of hyaluronic acid such as intra-articular and ocular applications.

In contrast to the previously taught methods for preparing ready-to-use pharmaceutical formulations of hyaluronic acid, the inventor of the present application has developed, for the first time, a process which enables the provision of sterile ready-to-use pharmaceutical formulations of high molecular weight HA that can be directly filled into syringes or vials for pharmaceutical use directly from the process "reactor," with no further preparation or sterilization required before use. The process of the present invention avoids the problems of contamination due to storage, transport, weighing, measuring and mixing of separate, even sterile, components of the formulation, as in prior art methods; and avoids the need to accurately measure a specific amount of HA powder and water to be mixed to obtain the desired concentration of the formulation, since the concentration of the formulation is accurately monitored to arrive at the desired specified concentration during the vacuum concentration step. Further, the process of the present invention allows the preparation of a ready-to-use sterile pharmaceutical formulation in which the required properties of high molecular weight of hyaluronic acid and determined viscosity are maintained.

WO 00/44925 (of which US Patent No. 6,489,467 is the US national phase equivalent) is not in any way concerned with the preparation of a ready-to-use pharmaceutical formulation of high molecular weight hyaluronic acid salt at a specified concentration. Indeed, WO 00/44925 is directed to a process for obtaining a nominally sterile purified powder of high molecular weight sodium hyaluronate, and teaches that the dry sodium hyaluronate powder obtained by the method described therein "may be used for preparing pharmaceutical compositions" (see page 14, second paragraph and page 16, second paragraph of WO 00/44925).

The ordinarily skilled person wishing to prepare a ready-to-use pharmaceutical formulation of HA would understand, on reading WO 00/44925, that to produce a pharmaceutical formulation of sodium hyaluronate, it is first necessary to prepare a purified sterile concentrated powder of the sodium hyaluronate, according to the method described WO 00/44925, and that this powder may then be used for preparing ready-to-use pharmaceutical preparations in the conventional manner. That is to say, by weighing out a specific amount of the purified concentrated sodium hyaluronate powder, mixing this powder with a specific quantity of water, and filling vias and syringes ready for medical use. The ordinarily skilled person on reading WO 00/44925 would have no motivation to look to any other starting point for the preparation of a ready-to-use pharmaceutical composition.

Therefore, it cannot be considered obvious in any way from the teaching of WO 00/44925 (and accordingly of corresponding US Patent No. 6,489,467) to produce a ready-to-use sterile pharmaceutical formulation of defined concentration of high molecular weight HA by providing an aqueous formulation of high molecular weight HA at a concentration of less than the required concentration, passing the aqueous formulation through a filter having a poor size less than 0.45 μm followed by the boiling of water under vacuum until the pre-defined desired concentration of the pharmaceutical formulation is reached, all according to the process of the present invention as claimed. Accordingly, it is submitted that contrary to the Examiner's assertion, claims 1-6 of the present application cannot be considered obvious over the subject matter claimed in US Patent No. 6,489,467, and that the Examiner's non-statutory double-patenting rejection of claims 1-6 of the present application is respectfully traversed.

EP 0 631 799 discloses a vacuum concentration plant designed for carrying out the bulk concentration of liquids such as colorings on a large scale. EP 0 631 799 is not concerned in any way with the preparation of pharmaceutical formulations ready for use, and does not provide any teaching whatsoever to enable the preparation of a sterile ready-to-use pharmaceutical formulation having a pre-determined specified concentration of hyaluronic acid salt, i.e. that would be suitable for directly into recipients (i.e. syringes and vials) for medical application.

It is highlighted that EP 0 631 799 is not concerned with providing a product solution having a precise, pre-determined, concentration necessary for medical applications. EP 0 631 799 does not describe or suggest any means that would allow the monitoring of the concentration of the liquid in the vacuum evaporator during the concentration process, nor for stopping the vacuum evaporation concentration process abruptly when the desired concentration of substrate has been reached, so as to be able to provide an aqueous solution of hyaluronic acid salt having a specific concentration, within a very narrow limit of variations, required for medical use.

As discussed above, the ordinarily skilled person on reading WO 00/44925 would understand that to produce a pharmaceutical formulation of sodium hyaluronate, it is first necessary to prepare a purified sterile concentrated powder of the sodium hyaluronate, and that this powder may then be used for preparing pharmaceutical formulations, in a conventional manner.

The ordinarily skilled person on reading WO 00/44925 would have no reason whatsoever to look to the teaching of EP 0 631 799. Even if the ordinarily skilled person inventively looked to EP 0 631 799, he would not arrive at the invention as claimed, since EP 0 631 799 makes no mention whatsoever of the provision of ready-to-use sterile pharmaceutical formulations directly fillable from the vacuum evaporator into syringes and vials for direct medical use, and does not allow one to arrive at a specific desired concentration during the vacuum evaporation operation, and does not teach a sterile system.

There is nothing in either of the cited prior art documents that would suggest to the ordinarily skilled person to prepare a ready-to-use high molecular weight hyaluronic acid salt

pharmaceutical formulation by filtering a low concentration solution of HA through a filter of poor size less than 0.45 μm followed by the boiling of water by the application of a vacuum until the pre-determined specified therapeutic concentration of HA is reached, all according to the claimed method of the present invention. There is also no teaching whatsoever that such a method would successfully allow the preparation of ready-to-use sterile solutions of high molecular weight HA at concentrations for therapeutic pharmaceutical use, without degradation of HA, or reduction of viscosity, and by avoiding the above-described drawbacks of the previously known methods for preparing ready-to-use pharmaceutical formulations of HA.

Accordingly, it is respectfully submitted that claims 1-9, as amended, are patentable over the teachings of the cited documents WO 00/44925 and EP 0 631 799, either alone or in combination.

For all of the foregoing reasons, Applicant respectfully requests entry of the foregoing amendments to the claims, reconsideration of the present application in light thereof and in light of the above remarks, and allowance of claims 1-9, as amended, over all the prior art of record.

Respectfully submitted,

By: _____

Clifford W. Browning
Reg. No. 32,201
Krieg DeVault LLP
One Indiana Square
Suite 2800
Indianapolis, IN 46204
(317) 238-6203